

Prenylamine in treatment of angina

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Forty-one patients with angina completed a double-blind cross-over trial in which the antianginal effects of prenylamine were compared with those of a placebo. Prenylamine produced a highly significant reduction in the frequency of anginal attacks, 32 patients reporting improvement. Prenylamine caused a slight but significant bradycardia and a small but significant reduction in diastolic blood pressure; but these changes had no statistical correlation with improvement in angina. It is concluded that prenylamine is a useful drug in the treatment of the majority of patients with angina though it is not effective in all.

Several clinical trials of prenylamine have reported symptomatic improvement in patients with angina (Winsor *et al.*, 1971; Stoker, 1968; Cardoe, 1970). The biochemical actions of prenylamine were fully reviewed in 1967 (*Biochemical Aspects of Prenylamine*, 1967). In spite of considerable knowledge about its biochemical effects, its mode of action in the relief of angina remains theoretical; Winsor and his colleagues (1971) discussed the possible mechanisms and concluded that the most likely explanation for its antianginal effect was an attenuation of adrenergic action on the heart.

This is a double-blind cross-over trial to assess the effects of prenylamine on angina pectoris.

Subjects and methods

Fifty-eight out-patients with a history of at least two months' angina of effort were admitted to the trial. All who were selected had been having at least six attacks of angina of effort a week. Patients who were satisfied with their previous antianginal treatment and those with clinical evidence of heart disease other than coronary disease were excluded as were those who were considered to be unable to co-operate. The nature of the trial was explained to those who entered and all gave their informed consent.

Before selection to the trial, a full history was taken and physical examination, chest x-ray, and 12 lead electrocardiogram were performed. If the resting electrocardiogram did not show ischaemic changes a two-step exercise test was performed for 5 minutes, unless chest pain or abnormal dyspnoea or fatigue occurred, when the exercise was stopped immediately. After the exercise test was stopped, a 12 lead electrocardiogram was re-

peated at minute intervals for 5 minutes. ST segment depression of at least 0.5 mm, which was sustained for at least 0.8 sec after the J point, was considered as a positive test. Patients who continued to have a normal post-exercise electrocardiogram were excluded from the trial.

The study was a double-blind cross-over trial in which the antianginal effect of prenylamine, 60 mg orally taken four times daily, was compared with that of a placebo (lactose tablets which were identical in appearance to the prenylamine tablets and were also taken four times daily). Patients were seen at monthly intervals. After a 2-month period on placebo tablets to familiarize patients with the pattern of the trial, they were randomly divided into two groups on a double-blind basis. One group took the drugs for monthly periods in the following order: prenylamine, placebo, prenylamine, placebo; the other group took the prenylamine and placebo in the reverse order.

The patients were asked to record at the end of each day the number of anginal attacks which they had had and the number of nitroglycerin tablets which they had taken. On entry to the trial those patients who had previously been taking nitroglycerin tablets prophylactically were asked to refrain from doing so throughout the course of the trial. At each monthly visit to the clinic the following observations were made: resting pulse rate and blood pressure, peak flow rate with a Wright peak meter (three measurements were made and the mean were recorded), and an exercise test consisting of stepping up and down a 23 cm high step, the rate of stepping being calculated from body weight so that each patient exercised at 300 kg m per min for 5 minutes. They were instructed to stop the exercise if chest pain, abnormal dyspnoea, or undue fatigue developed. When exercise was stopped early, the time and reason for this were recorded. The pulse rate was taken immediately after stopping exercise.

Of the 58 patients who were eligible for the trial, 17 had to be excluded. Eight patients who started did not complete the 4-month period of the trial for the follow-

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ing reasons: 2 patients developed myocardial infarction, 2 patients died, 1 patient developed left ventricular failure, 1 patient developed severe dermatitis, and 2 did not attend after their first visits. These patients were on placebo at the time of exclusion from the trial, 6 during the pre-allocation placebo period. Fifty patients completed the 6-month course and were therefore available for potential analysis. A further 9 patients, however, were excluded from the final analysis, 4 because they had had less than 4 attacks of angina throughout the course, 4 because they completed their record cards incorrectly, and 1 because he did not attend the clinic at the appropriate times. Information from 41 patients was, therefore, used in the final analysis; of these 35 were male and 6 were female. The mean age was 52.6 years with a range of 32 to 69 years. The mean weight was 76 kg, with a range of 55 to 105 kg. There was no statistically significant difference at the 5 per cent level (Student 't' test) in age, sex, cigarette consumption, weight, or frequency of anginal attacks before entering into the trial between the 41 patients who entered the final analysis and the 17 who were excluded.

Results

The results are a comparison of the last four months of the trial and are summarized in the

Table. The data for the two separate months while on prenylamine are compared with those for the two months on placebo treatment. There was no statistically significant difference between those who started their four-month alternating periods with prenylamine and those who started with placebo in relation to cigarette consumption, age, weight, and number of anginal attacks before entering into the trial.

Number of anginal attacks

During the placebo periods the mean incidence of anginal attacks per patient was 42.9 over two months. During treatment with prenylamine the mean incidence of anginal attacks was 33.7 over two months. This difference is significant ($P < 0.025$ by analysis of variance). There was a strong correlation ($r = 0.97$) between the number of anginal attacks and the number of nitroglycerin tablets taken. No separate analysis was, therefore, made of the significance between reduction in the intake of nitroglycerin tablets while on prenylamine and on placebo.

Of the 41 patients, 32 had fewer anginal attacks

TABLE *Summary of results for each month of trial*

Quantity observed	First placebo month		Second placebo month		First prenylamine month		Second prenylamine month	
	Mean	Standard Error	Mean	SE	Mean	SE	Mean	SE
Number of anginal attacks (41 patients)	46.4	12.8	39.4	8.9	38.4	11.5	29.1	6.5
Peak flow rate (41 patients)	413	14.7	415	14.3	426	14.5	418	15.5
Blood pressure								
systolic	146	3.3	145	3.7	140	3.9	139	3.7
diastolic (41 patients)	88	1.9	92	1.6	84	1.6	85	1.6
Pulse								
Before exercise	75	1.7	75	1.9	65	1.6	66	1.8
After exercise (31 patients who achieved a steady state exercise pulse by completing at least 1½ minutes of exercise)	92	2.7	93	2.2	86	2.4	85	2.5

Exercise performance

Results	No. of patients First placebo month	Second placebo month	First prenylamine month	Second prenylamine month
Completed 5 minutes of exercise	17	18	19	21
Stopped because of angina	18	18	16	14
Stopped because of fatigue	1	0	1	1
Stopped because of dyspnoea	5	5	5	5
Total	41	41	41	41
Mean duration of exercise (min)	3.36	3.45	3.49	3.74

when on the drug than when on placebo, 8 had more, and 1 showed no change. In 7 patients the incidence of angina was more than halved while on prenylamine.

During the exercise test there was improvement in the duration of exercise achieved in patients while on prenylamine but this was not significant at the 5 per cent level (χ^2 test).

The diminution in the incidence of angina showed no significant relation to the ages, weight, or cigarette consumption of the patients.

Heart rate

The mean resting heart rate in the patients while on placebo was 73 beats a minute, whereas while on prenylamine the mean rate was 66. This reduction is significant ($P < 0.001$ by analysis of variance). The mean pulse rate after exercise while on placebo was 93 a minute and while on prenylamine 85 a minute; the reduction in rate after exercise while on prenylamine is also significant ($P < 0.001$). Prenylamine therefore produced a significant but mild bradycardia effect, both at rest and after exercise. There was, however, no significant statistical correlation between the drop in pulse rate and the improvement in angina.

Blood pressure

The mean blood pressure in patients on placebo was 146/90 mmHg whereas on prenylamine it was 140/85 mmHg. Analysis of variance showed no significant difference between the systolic blood pressures ($P > 0.05$) but there was a significant difference between the diastolic pressures ($P < 0.01$). The decrease in diastolic blood pressure had no statistically significant correlation with improvement in angina.

Peak flow rate

There was no significant difference between the peak flow rates in patients while on prenylamine compared with those while on placebo.

Side effects

Of the patients who completed the trial, one patient developed fatigue while on prenylamine. This was not sufficiently severe to necessitate his exclusion from the trial. No gastrointestinal or other side effects were reported.

Discussion

These results indicate that prenylamine, given as 60 mg tablets four times daily, is an effective agent for diminishing the frequency of angina. The only side effect which occurred in this trial was fatigue in

one patient; this was not sufficiently pronounced to necessitate stopping the drug. Winsor and his colleagues (1971), and Stoker (1968) all reported a larger number of side effects including sedation, gastrointestinal symptoms and skin reactions; nevertheless in neither of these trials were the side effects common. Winsor *et al.* (1971) also found that the incidence of side effects in patients taking placebo was high.

The peak flow measurements were unchanged by the drug and there is, therefore, no evidence that prenylamine causes bronchial constriction; however, none of our patients had known preceding bronchial asthma. It, therefore, seems unlikely that prenylamine has the potential disadvantages of propranolol in the treatment of angina, namely a predisposition to heart failure and bronchial constriction (Matthews and Turck, 1969; Gaddie and Skinner, 1972).

Although the majority of patients showed a considerable reduction in the number of anginal attacks, and in some patients this reduction was striking, with the incidence of angina being more than halved, not all patients improved and in 8 patients the incidence of anginal attacks was increased while on the drug.

Much is known about the pharmacological action of prenylamine (*Biochemical Aspects of Prenylamine*, 1967), but the mechanism of its antianginal action is still uncertain. It seems probable that this is largely because of the inhibition of catecholamine uptake by storage granules (Carlsson and Waldeck, 1968) which leads to diminution in the catecholamine content of sympathetically innervated organs including the heart (Obianwu, 1965). However, it is known that even after a large dose there is still a considerable amount of noradrenaline remaining within the myocardium (Nielsen and Owman, 1967), but there is no pharmacological evidence to suggest that the effect of prenylamine lasts for more than a few days. In dogs intravenous prenylamine produces coronary vasodilatation (Braasch and Fleck, 1961) and an increase in coronary blood flow has been reported after intravenous injection in humans (Ito and Hasegawa, 1963). Prenylamine is not a beta-blocker and does not block the action of isoprenaline on cardiac beta-receptors (Hodge, 1969). It is known that prenylamine delays calcium transport in the sarcoplasmic reticulum (Schöne and Lindner, 1960), and it is possible that its antianginal effect is caused in part by its action on electro-mechanical coupling.

Winsor and his colleagues (1971) speculated about the mode of action of prenylamine in the relief of angina. The most likely explanation for its antianginal effect appeared to them to be due to

attenuation of the action of the sympathetic nervous system on the heart. They too found a diminution in heart rate and blood pressure. In this trial, however, neither the bradycardia effect nor the hypotensive effect showed any statistical correlation with the reduction in individual patients of the number of anginal attacks.

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References

- Biochemical Aspects of Prenylamine, Proceedings of Symposium, Capri* (1967). *Biochimica Applicata*, **14**, Suppl. 1.
- Braasch, W., and Fleck, D. (1961). The influence of prenylamine upon coronary blood flow and the oxygen supply of the myocardium. *Arzneimittel-Forschung*, **11**, 336.
- Cardoe, N. (1970). A two-year study of the efficacy and tolerability of prenylamine in the treatment of angina pectoris. *Postgraduate Medical Journal*, **46**, 708.
- Carlsson, A., and Waldeck, B. (1968). On the mechanisms of action of prenylamine on tissue monoamines. *Biochimica Applicata*, **14**, Suppl. 1, 41.
- Gaddie, J., and Skinner, C. (1972). Risk with beta-blocking in bronchial asthma. *British Medical Journal*, **1**, 749.
- Hodge, R. L. (1969). Investigation of a possible beta-blocking action of prenylamine in man. *Australian Journal of Experimental Biology and Medical Science*, **47**, 651.
- Ito, Y., and Hasegawa, Y. (1963). The effect of coronary vasodilators on the coronary circulation and the myocardial metabolism in sclerotic heart diseases. *Japanese Circulation Journal*, **27**, 164.
- Matthews, M. B., and Turck, W. P. G. (1969). Drugs in the management of angina pectoris. *Practitioner*, **202**, 230.
- Nielsen, K. C., and Owman, C. (1967). Differential amine depletion from cardiac adrenergic nerves by segontin. *Experimentia*, **23**, 203.
- Obianwu, H. O. (1965). The effect of prenylamine (Synadrin) on the amine levels of brain, heart and adrenal medulla in rats. *Acta Pharmacologica et Toxicologica*, **23**, 383.
- Schöne, H. H., and Lindner, E. (1960). The action of prenylamine on the metabolism of serotonin and noradrenalin. *Arzneimittel-Forschung*, **10**, 583.
- Stoker, J. B. (1968). Effect of prenylamine in angina pectoris. *British Journal of Clinical Practice*, **22**, 384.
- Winsor, T., Bleifer, K., Cole, S., Goldman, I. R., Karpman, H., Oblath, R., and Stone, S. (1971). A double-blind, double cross-over trial of prenylamine in angina pectoris. *American Heart Journal*, **82**, 43.

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